

15. (Amended) A method of determining [the] nucleotide sequences of a plurality of polynucleotides, the method comprising the steps of:

(a) attaching a first oligonucleotide tag from a repertoire of tags to each polynucleotide in a population of polynucleotides such that each first oligonucleotide tag from the repertoire is selected from a first minimally cross-hybridizing set of oligonucleotides between 12 and 60 nucleotides or basepairs in length and wherein each oligonucleotide of the first minimally cross hybridizing set differs from every other oligonucleotide of the first set by at least two nucleotides;

(b) sampling the population of polynucleotides to form a sample of polynucleotides such that substantially all different polynucleotides in the sample have different first oligonucleotide tags attached;

(c) sorting the polynucleotides of the sample by specifically hybridizing the first oligonucleotide tags with their respective complements, the respective complements being attached as uniform populations of substantially identical oligonucleotides in spatially discrete regions on the one or more solid phase supports;

(d) ligating one or more encoded adaptors to an end of identical copies of the polynucleotides in the sample, each encoded adaptor being a double stranded deoxyribonucleic acid comprising [having] a second oligonucleotide tag selected from a second minimally cross-hybridizing set of oligonucleotides between 8 and 20 nucleotides or basepairs in length and a protruding strand complementary to a protruding strand of a polynucleotide of the population, wherein each oligonucleotide of the second minimally cross hybridizing set differs from every other oligonucleotide of the second set by at least two nucleotides; and

(e) identifying a plurality of nucleotides in said protruding strands of the polynucleotides by specifically hybridizing a tag complement to each second oligonucleotide tag of the one or more encoded adaptors.

17. (Amended) A method of identifying a population of mRNA molecules, the method comprising the steps of:

(a) forming a population of cDNA molecules from the population of mRNA molecules such that each cDNA molecule has a first oligonucleotide tag attached, the first oligonucleotide tags being selected from a first minimally cross-hybridizing set of oligonucleotides between 12 and 60 nucleotides or basepairs in length and wherein each oligonucleotide of the first minimally cross hybridizing set differs from every other oligonucleotide of the first set by at least two nucleotides;

(b) sampling the population of cDNA molecules to form a sample of cDNA molecules

such that substantially all different cDNA molecules have different first oligonucleotide tags attached;

(c) sorting the cDNA molecules by specifically hybridizing the first oligonucleotide tags with their respective complements, the respective complements being attached as uniform populations of substantially identical complements in spatially discrete regions on one or more solid phase supports;

a³
(d) ligating one or more encoded adaptors to an end of the cDNA molecules in the population, each encoded adaptor being a double stranded deoxyribonucleic acid comprising [having] a second oligonucleotide tag selected from a second minimally cross-hybridizing set of oligonucleotides between 8 and 20 nucleotides or basepairs in length and a protruding strand complementary to a protruding strand of a cDNA molecule of the sample, wherein each oligonucleotide of the second minimally cross hybridizing set differs from every other oligonucleotide of the second set by at least two nucleotides; and

(e) determining the identity and ordering of a plurality of nucleotides in each of said protruding strands of the cDNA molecules by specifically hybridizing a tag complement to each second oligonucleotide tag of the one or more encoded adaptors;

wherein the population of mRNA molecules is identified by the frequency distribution of the portions of sequences of the cDNA molecules.

19. (Amended) A method of determining ~~the~~ a nucleotide sequence at an end of a polynucleotide, the method comprising the steps of:

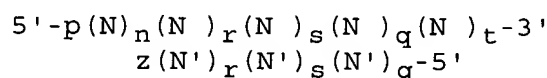
a⁴
(a) ligating an encoded adaptor to an end of the polynucleotide, the encoded adaptor being a double stranded deoxyribonucleic acid comprising [having] an oligonucleotide tag selected from a minimally cross-hybridizing set of oligonucleotides between 8 and 20 nucleotides or basepairs in length and a protruding strand complementary to a portion of a strand of the polynucleotide, wherein each oligonucleotide of the second minimally cross hybridizing set differs from every other oligonucleotide of the second set by at least two nucleotides;

(b) identifying one or more nucleotides in the portion of the strand of the polynucleotide by specifically hybridizing a tag complement to the oligonucleotide tag of the encoded adaptor ligated thereto;

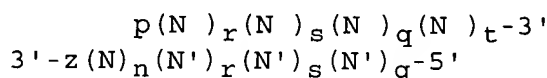
(c) cleaving the encoded adaptor from the end of the polynucleotide with a nuclease having a nuclease recognition site separate from its cleavage site so that a new protruding strand is formed at the end of the polynucleotide; and

(d) repeating steps (a) through (c).

24. (Amended) A composition of matter comprising a double stranded oligonucleotide adaptor having the form:



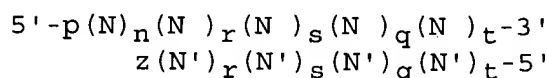
or



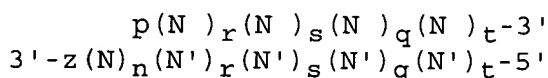
where N is a nucleotide and N' is its complement, p is a phosphate group, z is a 3' hydroxyl or a 3' blocking group, n is an integer between 2 and 6, inclusive, r is an integer between 0 and 18, inclusive, s is an integer which is either between four and six, inclusive, whenever the encoded adaptor has a nuclease recognition site or is 0 whenever there is no nuclease recognition site, q is an integer greater than or equal to 0, and t is an integer greater than or equal to 8 such that (N)_t is a single stranded moiety.

25. (Amended) The composition of claim 24 wherein r is between 0 and 12, inclusive, t is an ~~integer~~ integer between 8 and 20, inclusive, z is a phosphate group, and said single stranded moiety (N)_t is a member of a minimally cross-hybridizing set of oligonucleotides such that each oligonucleotide of the set differs from every other oligonucleotide of the set by at least two nucleotides.

27. (Amended) A composition of matter comprising a double stranded oligonucleotide adaptor having the form:



or



where N is a nucleotide and N' is its complement, p is a phosphate group, z is a 3' hydroxyl or a 3' blocking group, n is an integer between 2 and 6, inclusive, r is an integer between 0 and 18, inclusive, s is an integer which is either between four and six, inclusive, whenever the encoded adaptor has a nuclease recognition site or is 0 whenever there is no nuclease recognition site, q is